REMARKS

Claims 20-33 were pending in the subject application. Applicants have hereinabove amended claims 20, 25 and 31 and added new claims 42-54. Support for the amendments to these claims may be found, *inter alia*, as follows: claims 20 and 42 : page 9, lines 3-13; page 10 line 29 - page 11, lines 2; page 13, lines 16-22 and page 61, lines 3-5; table 2 on page 52, page 8, lines 23-24, page 35, lines 24-25 and page 51, lines 18-19; claims 25 and 47: page 10, lines 9 - 27; page 10 line 29 - page 11, line 8, page 8, lines 23-24, page 35, lines 24-25 and page 51, lines 18-19; claims 31 and 52 : page 11, lines 17-22, page 13, lines 16-22; table 2, page 52, page 8, lines 23-24, page 35, lines 24-25 and page 51, lines 18-19, claims 43 and 48: page 11, lines 10-15; claims 44 and 49: page 11, lines 17-23; claims 45 and 50: Page 12, lines 11-21; claims 46 and 51: page 12, line 28 to page 13, lines 1; claim 53: Page 11, lines 14-15 and page 13, lines 24-27; and claim 54: page 13, lines 29-32. Applicants maintain that these amendments raise no issue of new matter. Upon entry of this amendment, claims 20-33 and 42-54 will be pending and under examination.

Rejection Under 35 U.S.C. § 103

The Examiner stated that applicants' arguments in the Amendment filed October 31, 2007 have been fully considered but were not found persuasive. The Examiner asserted that the unexpected results are not commensurate in scope with the patent protection sought by applicants. Specifically, the Examiner asserted that the results are of *in vitro* cell proliferation assay, whereas the claims are drawn to *in vivo* methods. The Examiner asserted that while the *in vitro* cell proliferation results are no doubt unexpected, they are not commensurate in scope with the claims. The Examiner asserted that the only *in vivo* result is drawn to a single tumor cell line, TU-138 (head and neck squamous cell carcinoma) but alleged that these results do not appear to demonstrate statistically significant superior growth inhibition resulting from the combination of paclitaxel and C_6-ceramide as compared with each of paclitaxel and C_6-ceramide alone.

The Examiner rejected claims 20, 25, 30-31 under 35 U.S.C. §103(a) as allegedly unpatentable over Jayadev et al., (J. Biol. Chem. 1995, Vol. 270, pages 2047-2052) in view of Mycek et al. (Lippincott's Illustrated Review: Pharmacology 2nd Edition, 1997, pages 376 and 390-392). The Examiner asserted that the central issue remaining in the present case is whether or not the skilled artisan would have been motivated to administer a combination of paclitaxel and C_6-ceramide to treat cancer. The Examiner stated that applicants' arguments in the Amendment filed October 31, 2007 have been fully considered but failed to persuade the Examiner. The Examiner asserted that it would have been prima facie obvious to one of ordinary skill in the art to combine the teachings of Jayadev et al. in view of Mycek et al. Specifically, the Examiner asserted that one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success that by administering C_6-ceramide in combination with paclitaxel as taught by Jayadev et al. in view of Mycek et al., one would achieve a method of treating cancer.

The Examiner rejected claims 20-41 under 35 U.S.C. §103(a) as allegedly unpatentable over Spencer et al (Drugs, 1994, vol. 48, pages 794-847) in view of Cai et al (J. Biol. Chem., 1997, vol.272, pages 6918-6926). As discussed above, the Examiner asserted that the central issue remaining in the present case is whether or not the skilled artisan would have been motivated to administer a combination of paclitaxel and C_6-ceramide to treat cancer. The Examiner asserted that a prima facie case of obviousness has been established.

In response, applicants respectfully traverse the Examiner's ground of rejection.

Applicants Invention

As an initial matter, applicants' note that claims 20-33 are directed to head and neck squamous cell carcinoma cells, whereas new claims 42-54 are directed to pancreatic cancer cells. Specifically, applicants'

invention provides a method for inhibiting growth of a tumor comprising head and neck squamous carcinoma cells (as recited in amended claim 20) or pancreatic cancer cells (as recited in new claim 42), which method comprises contacting the tumor with (a) an amount of paclitaxel, and (b) an amount of C_6-ceramide, sequentially or concomitantly, wherein the amount of paclitaxel and the amount of C_6-ceramide in combination are effective to induce at least 50% growth inhibition of the tumor thereby inhibiting the growth of the tumor.

Applicants' invention also provides a method of decreasing the size of a tumor, comprising tumor cells, wherein the tumor cells head and neck squamous cell carcinoma cells (as recited in amended claim 25) or pancreatic cancer cells (as recited in new claim 45), which method comprises contacting the tumor with (a) an amount of paclitaxel (b) an amount of C_6-ceramide, sequentially or concomitantly, wherein the amount of paclitaxel and the amount of C_6-ceramide in combination are effective to induce apoptosis of the tumor cells, and wherein the decrease in size of the tumor is greater than the decrease in size caused by contacting the tumor with either paclitaxel alone or C_6-ceramide alone, thereby decreasing the size of the tumor.

Further, applicants' invention provides a method for treating a subject afflicted with head and neck squamous cell cancer (as recited in amended claim 31) or pancreatic cancer (as recited in new claim 52), which method comprises administering to the subject an amount of paclitaxel and an amount of C_6-ceramide, sequentially or concomitantly, wherein the amount of paclitaxel and C_6-ceramide are effective in combination to induce at least a 50% growth inhibition of the cells of the cancer, thereby treating the cancer.

Claims 20-33(Head and Neck Squamous Carcinoma Cells)

Jayadev et al. disclose that C_6-ceramide induces a significant block in cell cycle progression accompanied by apoptosis in Molt-4 human leukemia cells. Jayadev et al. do not disclose the use of paclitaxel,

or any use of any other chemotherapeutic agent in combination with C_6-ceramide.

Mycek et al. disclose paclitaxel as a chemotherapeutic agent in combination therapy with other anticancer agents, but do not disclose C_6-ceramide as a possible anticancer agent. Mycek et al. disclose that paclitaxel has shown good activity against advanced ovarian cancer and metastatic breast cancer and has shown favorable results in small-cell lung cancer, squamous-cell carcinoma of the head and neck and "several other cancers". While Mycek et al. disclose that the combination therapy of paclitaxel with other anticancer drugs is being evaluated, they do not disclose the specific combination of paclitaxel with C_6-ceramide.

None of Jayadev et al. or Mycek et al. disclose that C_6-ceramide inhibits growth of head and neck squamous carcinoma cells (amended claim 20), or that C_6-ceramide is effective to decrease the size of a head and neck squamous carcinoma cells (amended claim 25), or even that C_6-ceramide can be used for treating head and neck squamous cell carcinoma (amended claim 31). Moreover, neither of these references disclose any expected results of combination therapy with paclitaxel and C_6-ceramide. Therefore the combination of Jayadev et al. with Mycek et al. does not render obvious applicants invention as recited in claims 20-33.

With respect to the rejection under 103(a) of Spencer et al. in view of Cai et al., applicants' note that Spencer et al. disclose paclitaxel as an anticancer agent with broad-spectrum anticancer activity, including breast carcinoma, colon carcinoma, head and neck squamous cell carcinoma, leukemia, pancreatic carcinoma and prostate cancer. Spencer et al. further disclose combination therapy comprising paclitaxel and several other anticancer agents, but do not disclose combination therapy with C_6-ceramide. Spencer et al. do not disclose C_6-ceramide as an anticancer agent.

Cai et al. teach C_6-ceramide induces apoptosis in both TNF-sensitive and TNF-resistant breast cancer cells, but does not teach the combination of C_6-ceramide with paclitaxel or any other anticancer agent. Therefore, applicants maintain that the combination of Spencer et al. with Cai et al. does not render obvious applicants' claimed invention.

None of Spencer et al. or Cai et al. disclose that C_6-ceramide inhibits growth of head and neck squamous carcinoma cells (amended claim 20), or that C_6-ceramide is effective to decrease the size of a head and neck squamous carcinoma cells (amended claim 25), or even that C_6-ceramide can be used for treating head and neck squamous cell carcinoma (amended claim 31). Moreover, neither of these references disclose any expected results of combination therapy with paclitaxel and C_6-ceramide Therefore the combination of Spencer et al. with Cai et al. does not render obvious applicants invention as recited in claims 20-33.

In view of the above remarks, applicants maintain that the combination of either Jayadev et al. in view of Mycek et al. or Spencer et al. in view of Cai et al. does not render applicants' claimed invention obvious. Specifically, even if the Examiner has established a prima facie case of obviousness, to which applicants do not concede, applicants maintain that the specification discloses that paclitaxel in combination with C_6-ceramide produce unexpected results.

Specifically, page 51 of the instant specification discloses, *inter alia*, that Tu138 (head and neck squamous carcinoma cells) were implanted subcutaneously in nude mice, i.e. *in vivo*, which were treated beginning of day 4 with thrice weekly injections of paclitaxel 120 μg/0.1ml, alone, C_6-ceramide, 500 μg in 0.2ml, alone, combinations thereof and control. As shown in Figures 11 and 12, tumor growth was significantly inhibited by combination of paclitaxel and ceramide. For example, in Figure 11, after five weeks of treatment, the average size of tumor was just over 50 $(mm)^2$ in the case of treatment with combination paclitaxel and C_6-ceramide. In contrast, the average size

of tumor was just under 100 $(mm)^2$ for C_6-ceramide alone and just under 250 $(mm)^2$ for paclitaxel alone. In addition, the specification discloses that in human Tu138 head and neck squamous carcinoma cells lines, paclitaxel in combination with C_6-ceramide inhibited growth of the Tu138 cells by 66% as compared to growth inhibition of only 10% and 28% upon administration of each of paclitaxel and C_6-ceramide alone.

Accordingly, applicants have demonstrated *in vivo* an unexpected effect on growth inhibition of head and neck squamous carcinoma cells with the combination of paclitaxel and C_6-ceramide.

Applicants maintain that the unexpected results further render unobvious applicants invention as recited in claims 20-33 over Jaydev et al. in view of Mycek et al. and also over Spencer et al. in view of Cai et al.

In view of these remarks, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection with respect to claims 20-33.

Claims 42-54 (Pancreatic Cancer Cells)

Applicants have hereinabove added new claims 42-54. Applicants will address the Examiner's rejection of claims 20-33 with respect to new claims 42-54.

As noted above, Jayadev et al. disclose that C_6-ceramide induces a significant block in cell cycle progression accompanied by apoptosis in Molt-4 human leukemia cells. Jayadev et al. do not disclose the use of paclitaxel, or any use of any other chemotherapeutic agent in combination with C_6-ceramide.

Mycek et al. disclose paclitaxel as a chemotherapeutic agent in combination therapy with other anticancer agents, but do not disclose C_6-ceramide as a possible anticancer agent. Mycek et al. disclose that

paclitaxel has shown good activity against advanced ovarian cancer and metastatic breast cancer and has shown favorable results in small-cell lung cancer, squamous-cell carcinoma of the head and neck and "several other cancers". While Mycek et al. disclose that the combination therapy of paclitaxel with other anticancer drugs is being evaluated, they do not disclose the specific combination of paclitaxel with C_6-ceramide. Mycek et al. do not disclose paclitaxel as therapy for pancreatic cancer.

None of Jayadev et al. or Mycek et al. disclose that C_6-ceramide inhibits growth of pancreatic cancer cells (new claim 42), or that C_6-ceramide is effective to decrease the size of pancreatic cancer cells (new claim 47), or even that C_6-ceramide can be used for treating pancreatic cancer (new claim 52). Moreover neither reference discloses paclitaxel for use in treating pancreatic cancer. Finally, neither of these references disclose any expected results of combination therapy with paclitaxel and C_6-ceramide. Therefore the combination of Jayadev et al. with Mycek et al. does not render obvious applicants invention as recited in new claims 42-54.

With respect to the rejection under 103(a) of Spencer et al. in view of Cai et al., applicants note that Spencer et al. disclose paclitaxel as an anticancer agent with broad -spectrum anticancer activity, including breast carcinoma, colon carcinoma, head and neck squamous cell carcinoma, leukemia, pancreatic carcinoma and prostate cancer. Spencer et al. further disclose combination therapy comprising paclitaxel and several other anticancer agents, but do not disclose combination therapy with C_6-ceramide. Spencer et al. do not disclose C_6-ceramide as an anticancer agent.

Cai et al. teach C_6-ceramide induces apoptosis in both TNF-sensitive and TNF-resistant breast cancer cells, but does not teach the combination of C_6-ceramide with paclitaxel or any other anticancer agent. Therefore, applicants maintain that the combination of Spencer et al. with Cai et al. does not render obvious applicants' claimed

invention.

None of Spencer et al. or Cai et al. disclose that C_6-ceramide inhibits growth of pancreatic cancer cells (new claim 42), or that C_6-ceramide is effective to decrease the size of pancreatic cancer cells (new claim 47), or even that C_6-ceramide can be used for treating pancreatic cancer(new claim 52). Moreover, neither of these references disclose any expected results of combination therapy with paclitaxel and C_6-ceramide. Therefore the combination of Spencer et al. with Cai et al. does not render obvious applicants invention as recited in new claims 42-54.

In addition, applicants maintain that the specification discloses that paclitaxel in combination with C_6-ceramide produce unexpected results.

Specifically, the specification discloses on page 52, in Table 2, that in RWP-2 human pancreatic cell lines, paclitaxel and C_6-ceramide inhibited growth of the RWP-2 cells bys 75% as compared to growth inhibition of only 2% and 6% with administration of each of the agents alone, respectively.

In further support of unexpected results, applicants attach hereto as **Exhibit 1** a Declaration Under 37 C.F.R. §1.132 of Dr. Harold Wanebo, M.D., a co-inventor named in the subject application. In the Declaration, Dr. Wanebo declares the following:

1. That he and/or Shashikant Mehta and/or individuals acting under their direction performed the following *in vivo* experiments to test the combined effects of paclitaxel ("taxol") and C_6-ceramide. SCID/Beige/Taconic male mice (22-25 grams, 6-8 weeks old) (Taconic Laboratory, Germantown, NY, USA) were each inoculated with 2×10^6 L3.6 human pancreatic adenocarcinoma ("PA") cells subcutaneously in the internal surface of the right thigh. Four days later, when the mice developed primary tumors, chemotherapy was commenced by

injecting the mice intra-peritoneally with C_6-ceramide (also referred to as "ceramide 6") (10.0 mg/kg) alone (Group 2), taxol, i.e. paclitaxel (3.0 mg/kg) alone (Group 3), oxaliplatin (2.5 mg/kg) alone (Group 4), cis-platinum (also referred to as "cisplatin") (2.5 mg/kg) alone (Group 5), or combinations of taxol and C_6-ceramide (Group 6), oxaliplatin and C_6-ceramide (Group 7), and cis-platinum and C_6-ceramide (Group 8). The control group (Group 1) contained mice receiving no chemotherapeutic agent. The mice were treated 3 times per week for 4 weeks, and were observed for 6 weeks after commencing chemotherapy. The experimental results discussed below are those obtained with respect to Groups 1, 2, 3 [sic], and 6 [sic], even though data with respect to the remaining Groups are shown in the Exhibits annexed hereto.

2. Survival percentage rates among mice in Groups 1-8 were determined. As shown in **EXHIBIT B**, all mice in the control group (Group 1) died by the third week. All mice receiving C_6-ceramide alone (Group 2) died by the fourth week. All mice receiving taxol alone (Group 3) died by the fourth week of observation. In contrast, 60% of the mice receiving a combination of taxol and C_6-ceramide (Group 6) were still alive as of the sixth week.

3. Mean survival times ("MST") among the mice in Groups 1-8 were determined. As shown in **EXHIBIT C**, the mice in the control group (Group 1) had a MST of approximately 17.8 days; the mice receiving C_6-ceramide alone (Group 2) had a MST of approximately 20.8 days; the mice receiving taxol alone (Group 3) had a MST of approximately 23.0 days; and the mice receiving a combination of taxol and C_6-ceramide (Group 6) had a MST of approximately 35.2 days.

4. Tumor volumes among the mice in Groups 1-8 were determined. As shown in **EXHIBIT D**, the mice in the control group (Group 1)

had tumors with a mean tumor volume ("MTV") of approximately 1.56 cm^3; the mice receiving C_6-ceramide alone (Group 2) had tumors with a MTV of approximately 1.69 cm^3; the mice receiving taxol alone (Group 3) had tumors with a MTV of approximately 1.83 cm^3; and the mice receiving a combination of taxol and C_6-ceramide (Group 6) had tumors with a MTV of approximately 1.19 cm^3.

5. The mean rate of tumor development ("MRTD"), which indicates the speed of tumor development, was measured among the mice in Groups 1-8 using the formula MTV/MST. As shown in **EXHIBIT E**, the mice in the control group (Group 1) had a MRTD of approximately 0.086 cm^3/day; the mice receiving C_6-ceramide alone (Group 2) had a MRTD of approximately 0.082 cm^3/day; the mice receiving taxol alone (Group 3) had a MRTD of approximately 0.078 cm^3/day; and the mice receiving a combination of taxol and C_6-ceramide (Group 6) had a MRTD of approximately 0.035 cm^3/day.

6. The mean weight of tumor ("MWT") among the mice in Groups 1-8 was determined. As shown in **EXHIBIT F**, the mice in the control group (Group 1) had a MWT of approximately 1.56 grams; the mice receiving C_6-ceramide alone (Group 2) had a MWT of approximately 1.04 grams; the mice receiving taxol alone (Group 3) had a MWT of approximately 0.82 grams; and the mice receiving a combination of taxol and C_6-ceramide (Group 6) had a MWT of approximately 1.26 grams.

7. Mean body weight ("MBW") was measured every week for the mice in Groups 1-8. As shown in **EXHIBIT G**, the mice in the control group (Group 1) had a MBW of approximately 17.2 grams; the mice receiving C_6-ceramide alone (Group 2) had a MBW of approximately 17.0 grams; the mice receiving taxol alone (Group 3) had a MBW of approximately 17.4 grams; and the mice

receiving a combination of taxol and C_6-ceramide (Group 6) had a MBW of approximately 20.0 grams.

As shown in **Exhibit B**, mice receiving paclitaxel (taxol) alone or C_6 ceramide alone all died by the fourth week of treatment. In contrast, 60% of mice were still alive after 6 weeks of treatment when paclitaxel and C_6-ceramide were administered in combination. Moreover, as shown in **Exhibit C,** the mean survival time of mice receiving control treatment was 17.8 days. Mice receiving paclitaxel (taxol) alone had a mean survival time of 20.8 days and mice receiving C_6-ceramide alone has a mean survival time of 23.0 days. In contrast, mice receiving a combination of paclitaxel and C_6-ceramide had a mean survival time of 35.2 days. In addition, the mean rate of tumor development (cm3/day), as shown in **Exhibit D**, was 0.086 for mice receiving control treatment. Mice receiving C_6-ceramide alone was 0.082 and 0.078 for mice receiving paclitaxel alone. In contrast, the mean rate of tumor development in mice receiving a combination of paclitaxel and C_6-ceramide was 0.035. In addition, the specification discloses on page 52, in Table 2, that in RWP-2 human pancreatic cell lines, paclitaxel and C_6-ceramide inhibited growth of the RWP-2 cells bys 75% as compared to growth inhibition of only 2% and 6% with administration of each of the agents alone, respectively.

Accordingly, applicants have demonstrated *in vivo* an unexpected effect on growth inhibition of pancreatic cancer cells with the combination of paclitaxel and C_6-ceramide.

Accordingly, applicants maintain these unexpected results further render nonobvious the applicants' invention, as recited in new claims 42-54, over Jayadev et al. in view of Mycek et al and also over Spencer et al. in view of Cai et al.

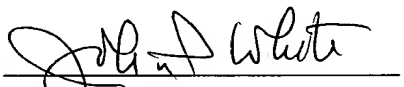
Conclusion

In view of the remarks hereinabove, applicants respectfully submit that the grounds of rejection set forth in the February 15, 2008 Office Action have been overcome. Applicants therefore respectfully request that the Examiner reconsider and withdraw these grounds of rejection and allow claims 20-33 and 42-54.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fees, other than the $525.00 three-month extension fee and $25.00 additional claims fee, is deemed necessary in connection with the filing of this Amendment. Accordingly, a check in the amount of $550.00 is enclosed. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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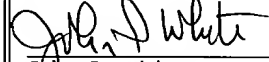

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